Multimodal Imaging Mass Spectrometry for Probing Aβ-Plaque Pathology in Transgenic Alzheimer's Disease Mice

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Alzheimer's disease is the most common neurodegenerative disorder affecting 12% over 65 (1). The exact mechanisms underlying AD pathogenesis are still not fully understood, significantly hampering the development of therapeutic treatment strategies. In AD, cognitive decline has been linked to formation of β-amyloid (Aβ) deposits as senile plaques as well as intracellular neurofibrillary tangles comprised of hyper-phosphorylated tau protein (2). Aβ aggregation has been suggested as a possibly critical, early inducer driving the disease progression. Over the years several transgenic mouse models have been developed, since the neuropathology in genetic- and sporadic AD is similar with respect to protein accumulation (1). The arctic and swedish mutation (ARCSWE) of amyloid precursor protein (APP) results in significant increase of neurotoxic Aβ peptides and fibrils (3).

Changes in amyloid peptide truncation and plaque associated neuronal lipid species have been implicated with proteopathic mechanisms in AD (1,4).Current biochemical methods however lack the neccessary molecular specificity to study plaque chemistry, highlighting the need to develop and employ new bioanalytical techniques such as imaging mass spectrometry (IMS) (5).

The aim of this study was therefore to employ SIMS and MALDI based multimodal imaging mass spectrometry to probe Aβ plaque pathology in tgARCSWE mice with particular focus on associated neuronal lipid species and Aβ peptide truncation.

Transgenic C57BL/6-CBA-F1 male mice carrying the swedish double mutation alone (K670M, N671L) and the Arctic mutation (E693G) of human APP were studied. Lipid changes were examined in adult mouse brain (18 month) using ToF-SIMS and MALDI imaging on fresh frozen coronal cryosections at two different bregma (CPu and Hippocampus).

SIMS IMS revealed localizations of distinct lipid species in different brain regions in transgenic AD animals including sulfatides, triglycerides and cholesterol. Consecutive MALDI IMS identifies beta amyloid containing plaques as well as AD implicated Aβ peptide truncation (pyro-Glu). High resolution SIMS imaging performed in burst aligned mode, shows localization of phospholipids and cholesterol to these amyloid plaques in AD mice (Fig.1). This implicates a prominent role for cholesterol in promoting neurotoxic protein accumulation.

In conclusion, SIMS and MALDI based multimodal imaging is therefore a promising approach to interrogate chemical plaque pathology in Alzheimer's disease.

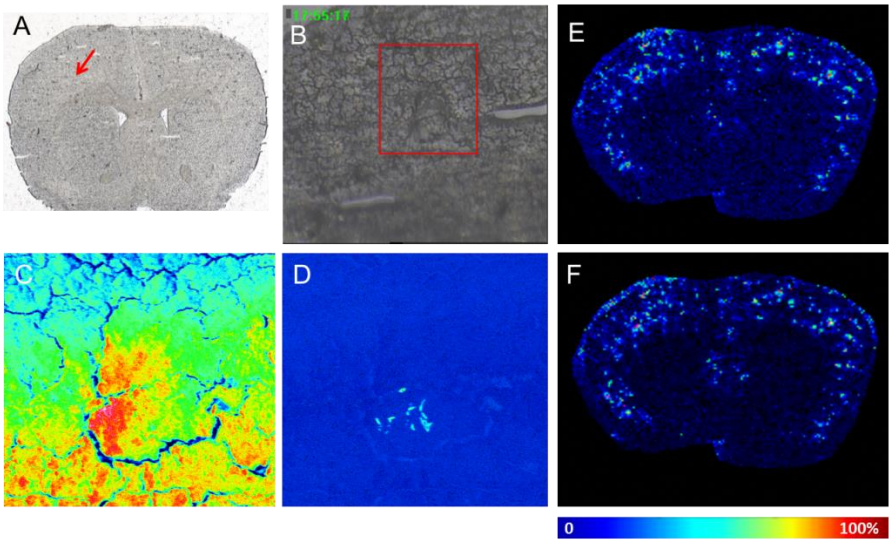

Figure 1: Multimodal Imaging for characterizing the plaque pathology in transgenic Alzheimer mice. Coronal tissue cryosections from 18 month old ARCSWE mice that displayed extensive plaque pathology (A, magnification 3B) were analyzed using high resolution SIMS imaging of individual Aβ plaques. SIMS analysis revealed localization of phosphocholine (PC) lipids to the plaque as indicated by the PC-headgroup (C, single ion image of m/z 184.09, size: 512x512µm). Characteristic localization of cholesterol (m/z 369.33) to the center of the plaque was observed (D) as revealed by multivariate image analysis using maximum autocorrelation factor analysis. (E,F) MALDI imaging analysis of the same tissue section revealed the Aβ peptide chemistry in these plaques. Different truncations (E, Aβ1-40 and F, Aβ 3pE-40) were observed, including the 3-pyroglutamate truncation (Aβ 3pE-40), which is considered very neurotoxic and promotes extensively oligomerization.

References:

(1) Selkoe, D.J. and Schenk D., *Annu Rev Pharmacol Toxicol*, 2003.43: p. 545-84

(2) Thal D.R. et al., *Neurology*, 2002. 58(12): p. 1791-800

(3) Lord, A., et al., *Neurobiol Aging*, 2006. 27(1): p. 67-77

(4) Di Paolo G. and Kim TW, *Nat Rev Neurosci*, 2011, 12(5): p.284-296

(5) Hanrieder J. et al. *ACS Chem Neurosci*, 2014, 5(7): p.568-575